

1000
900
800
700
600
500
400
300
200
100
0

| | | | | | | | | | | | | | | | |
|--|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|----|
| GGCCTGACTACCAGAAAC | ATG | GCG | ACC | AGC | GCT | GTT | CCA | AGT | GAA | AAC | CTT | CCC | ACA | TAT | 60 |
| | M | A | T | S | A | V | P | S | E | N | L | P | T | Y | 14 |
| AAA CTA GTA GTG GTG GGA GAT GGT GGT GTG GGC AAG AGT GCG CTC ACT ATT CAG TTT TTC | 120 | | | | | | | | | | | | | | |
| K L V V V G D G G V G K S A L T I Q F F | 34 | | | | | | | | | | | | | | |
| CAG AAG ATC TTT GTG CCT GAC TAC GAC CCC ACC ATT GAA GAC TCC TAC CTG AAG CAT ACA | 180 | | | | | | | | | | | | | | |
| Q K I F V P D Y D P T I E D S Y L K H T | 54 | | | | | | | | | | | | | | |
| GAG ATT GAC AAT CAG TGG GCC ATC TTG GAT GTT CTG GAC ACA GCC GGG CAG GAG GAG TTC | 240 | | | | | | | | | | | | | | |
| E I D N Q W A I L D V L D T A G Q E E F | 74 | | | | | | | | | | | | | | |
| AGT GCC ATG CGG GAA CAA TAC ATG CGC ACA GGG GAT GGC TTC CTC ATT GTC TAC TCC GTC | 300 | | | | | | | | | | | | | | |
| S A M R E Q Y M R T G D G F L I V Y S V | 94 | | | | | | | | | | | | | | |
| ACC GAC AAG GCC AGC TTC GAG CAC GTG GAC CGC TTC CAC CAG CTC ATT CTG CGT GTC AAG | 360 | | | | | | | | | | | | | | |
| T D K A S F E H V D R F H Q L I L R V K | 114 | | | | | | | | | | | | | | |
| GAC AGG GAG TCA TTC CCA ATG ATC CTC GTG GCC AAC AAG GTG GAT CTG ATG CAC CTA AGG | 420 | | | | | | | | | | | | | | |
| D R E S F P M I L V A N K V D L M H L R | 134 | | | | | | | | | | | | | | |
| AAA GTC ACC AGG GAC CAA GGA AAA GAA ATG GCA ACC AAA TAC AAT ATC CCA TAT ATA GAG | 480 | | | | | | | | | | | | | | |
| K V T R D Q G K E M A T K Y N I P Y I E | 154 | | | | | | | | | | | | | | |
| ACC AGT GCC AAG GAC CCG CCT CTC AAC GTG GAT AAA ACC TTC CAT GAC CTA GTT AGA GTA | 540 | | | | | | | | | | | | | | |
| T S A K D P P L N V D K T F H D L V R V | 174 | | | | | | | | | | | | | | |
| ATT AGG CAA CAG GTT CCA GAG AAA AAC CAG AAG AAG AAA AAG AAG ACA AAA TGG CGA GGA | 600 | | | | | | | | | | | | | | |
| I R Q Q V P E K N Q K K K K K T K W R G | 194 | | | | | | | | | | | | | | |
| GAC AGG GCC ACC GGC ACT CAC AAA CTG CAG TGT GTC ATC TTG TGA CAG CCT GAA GCC CTG | 660 | | | | | | | | | | | | | | |
| D R A T G T H K L Q C V I L * | 208 | | | | | | | | | | | | | | |
| GGCATAGCAACCGTGAACCTGCCAGCCCCTGGGACCAGCCCCTGCCTAACTGCACTGAGAACCACCTTCTAACTACAGCC | 739 | | | | | | | | | | | | | | |
| CTTGGCTCTTGGACTGGGCATTGGAAGGGAATGAGGGAGGAGGGGGCAGAAGCAGGCCGGGGCTGGCTTTGCTGCCTGT | 818 | | | | | | | | | | | | | | |
| CCCAGGAGACAGGGCTACAGCTTCCAAACCTTTTGTGTGTTGACTGAGCCCAGTTCCAGTCTCTTGGTGGGCTTGTTT | 897 | | | | | | | | | | | | | | |
| CTTTTAACTCATAGGCTGGTTTGCTATGGAAGTGCTTACCCACATACAACGCACCAGACAAGCCATGAGCAAGCTTCCT | 976 | | | | | | | | | | | | | | |
| CCCTGTCCCATCCCCAGTGTCTGAGCTCTTGTGTCTTTTGTAGATTTTAAATTATTTGAGTAATGATTATTTTATTAA | 1055 | | | | | | | | | | | | | | |
| AGAGGTCTGTGCCCATTGCCCTGCGAAGCCCCAAGTCTTTGGCAGACCTCTGATAAATGTCTGCA | 1119 | | | | | | | | | | | | | | |

Figure 1

| | | |
|---------|--|-----|
| p21 Ras | MT-----EYKLVVVGAGGVGKSALTIQLI | 24 |
| M-Ras | MATSAV-----PSENLP--TYKLVVVGDDGGVGKSALTIOFF | 34 |
| R-Ras | MSSGAASGTGRGRPRGGGPGPRDPPPGETHKLVVVGGGGVGKSALTIOFI | 50 |
| p21 Ras | QNHFVDEYDPTIEDSYRKQVVIDGETCLLDYLDTAGQEEYSAMRDQYMRT | 74 |
| M-Ras | QKIFVPDYDPTIEDSYLKHTEIDNQWAILDVLDTAGQEEFSAMREQYMRT | 84 |
| R-Ras | QSYFVSDYDPTIEDSYTKICTVDGIPARLDILDLAGQEEFGAMREQYMRA | 150 |
| p21 Ras | GEGFLCVFAINNTKSFEDIHQYREQIKRVKDSDDVPMVLVGNKCDLAA-R | 123 |
| M-Ras | GDGFLIVYSVTDKASFEHVDRFHQLILRVKDRESFPMILVANKVDLMHLR | 134 |
| R-Ras | GNGFLLVFAINDRQSFNEVGKLFQILRVKDRDDFPIVLVGNKADLENQR | 150 |
| p21 Ras | TVESRQAQDLARSYGIPYIETSAK-TRQGVEDAFYTLVREIRQHKLRLN | 172 |
| M-Ras | KVTRDQGKEMATKYNIPYIETSAKDPPLNVDKTFHDLVRVIRQQVPEKNQ | 184 |
| R-Ras | QVLRSEASSFSASHHMTYFEASAK-LRLNVDEAFEQLVRAVRKYQEQLP | 199 |
| p21 Ras | PPDESGP----GCMSC---KCVLS | 189 |
| M-Ras | KKKKKTKWRGDRATGTHKLQCVIL | 208 |
| R-Ras | PSPPSAPRK--KDGGC---PCVLL | 218 |

Figure 2

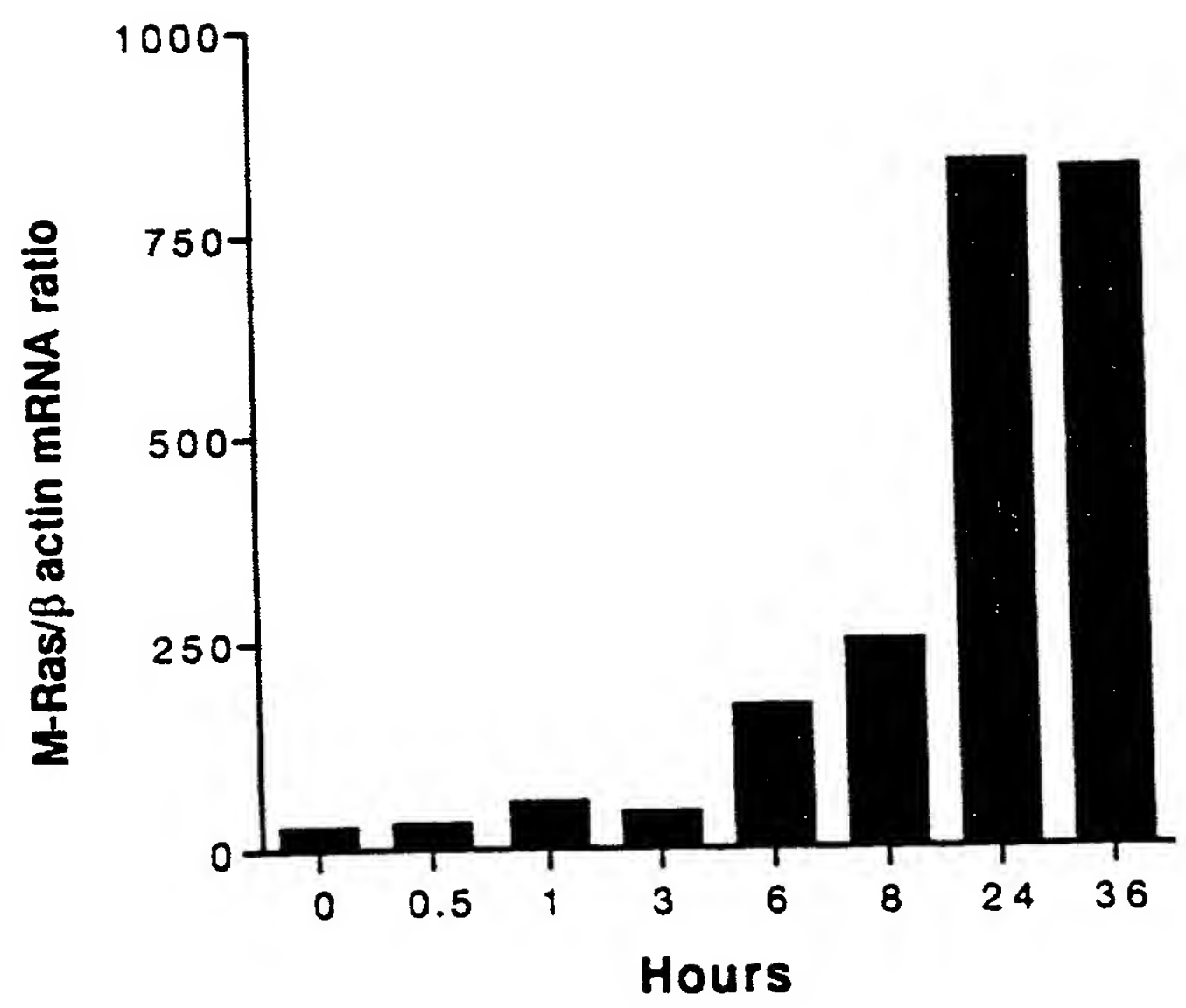
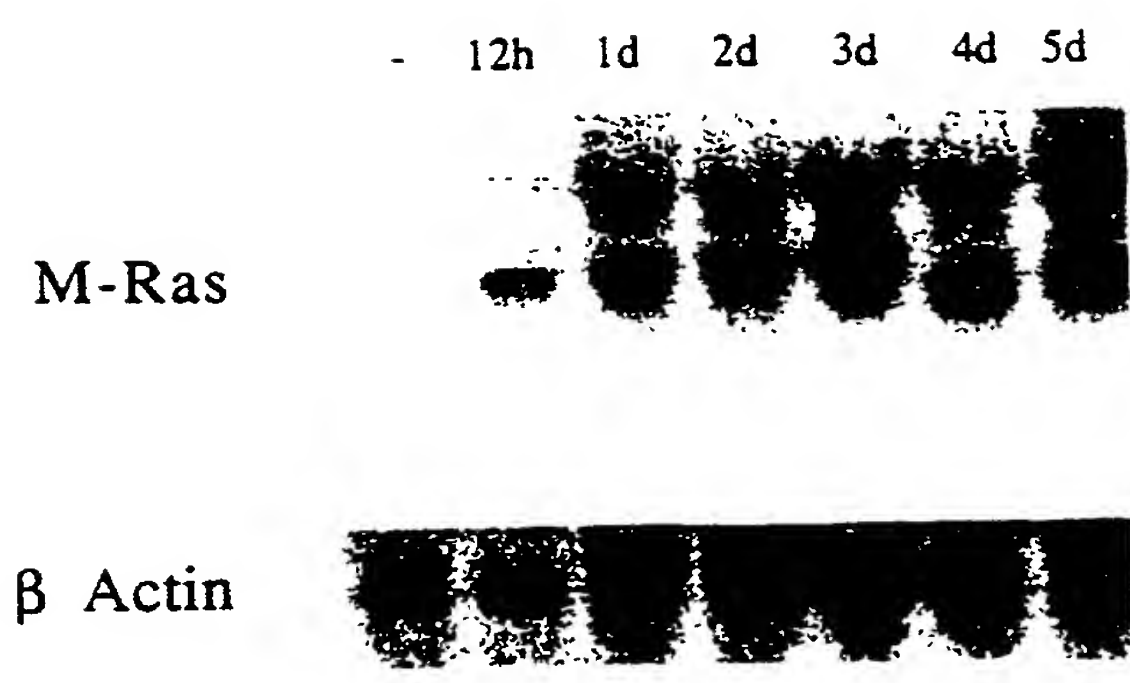


Figure 3

FVB

Liver
Kidney
Heart
Brain
Intestine
Spleen
Thymus
Lung
Bone Marrow

Tg5

Liver
Kidney
Heart
Brain
Intestine
Spleen
Thymus
Lung
Bone Marrow

Figure 4

| | | |
|--|-------------------------|------|
| CGGCGGCGACGCTGCCTCCTCACC | GGCGCAGGCTAGGAGGGGGCGG | 46 |
| CCTGAGTGCCGTAGCCGAGCCGGGGCTGGAGCGCGCGGTCTGACCTACGAGAAAC | ATG GCA ACC AGC GCC GTC | 120 |
| | M A T S A V | 6 |
| CCC AGT GAC AAC CTC CCC ACA TAC AAG CTG GTG GTG GTG GGG GAT GGG GGT GTG GGC AAA | | 180 |
| P S D N L P T Y K L V V V G D G G V G K | | 26 |
| AGT GCC CTC ACC ATC CAG TTT TTC CAG AAG ATC TTT GTG CCT GAC TAT GAC CCC ACC ATT | | 240 |
| S A L T I Q F F Q K I F V P D Y D P T I | | 46 |
| GAA GAC TCC TAC CTG AAA CAT ACG GAG ATT GAC AAT CAA TGG GCC ATC TTG GAC GTT CTG | | 300 |
| E D S Y L K H T E I D N Q W A I L D V L | | 66 |
| GAC ACA GCT GGG CAG GAG GAA TTC AGC GCC ATG CGG GAG CAA TAC ATG CGC ACG GGG GAT | | 360 |
| D T A G Q E E F S A M R E Q Y M R T G D | | 86 |
| GGC TTC CTC ATC GTC TAC TCC GTC ACT GAC AAG GCC AGC TTT GAG CAC GTG GAC CGC TTC | | 420 |
| G F L I V Y S V T D K A S F E H V D R F | | 106 |
| CAC CAG CTT ATC CTG CGC GTC AAA GAC AGG GAG TCA TTC CCG atG atC CTC GTG GCC AAC | | 480 |
| H Q L I L R V K D R E S F P M I L V A N | | 126 |
| AAG GTC GAT TTG ATG CAC TTG AGG AAG ATC ACC AGG GAG CAA GGA AAA GAA ATG GCG ACC | | 540 |
| K V D L M H L R K I T R E Q G K E M A T | | 146 |
| AAA CAC AAT ATT CCG TAC ATA GAA ACC AGT GCC AAG GAC CCA CCT CTC AAT GTC GAC AAA | | 600 |
| K H N I P Y I E T S A K D P P L N V D K | | 166 |
| GCC TTC CAT GAC CTC GTT AGA GTA ATT AGG CAA CAG ATT CCG GAA AAA AGC CAG AAG AAG | | 660 |
| A F H D L V R V I R Q Q I P E K S Q K K | | 186 |
| AAG AAG AAA ACC AAA TGG CGG GGA GAC CGG GCC ACA GGC ACC CAC AAA CTG CAA TGT GTG | | 720 |
| K K K T K W R G D R A T G T H K L Q C V | | 206 |
| ATC TTG TGA GGCCTGCAGGCCTGAAGGCCTCGGGCACAGTGACGGTGGCCTGGCCAGCCCTCGGGACCCCTCCCCA | | 791 |
| I L * | | 208 |
| CCTAACTGCACTGAAACCATTTCTAACCACAACCCCTTGGCCCAAGGACTTGGTACAGGAAGGGAGAAGGGCAGGTGGGC | | 870 |
| AGGGAGCAAGACAGGGTCTGGCTTTTGCCAAGAGGAAACGGGGCTTTTTCCACCTTCTTCAAAGAGACAAGGGAAGGCC | | 949 |
| ACCTGTTAAAGCAGGAAGCAGCATCAAGTTGCCCTTGGGCCCCCCCCATGTTGTTTGGATTTCAAACCGGGTTTCCTTC | | 1028 |
| CCCTTCTTTTCGGGTTGGGTGTTGTTGGTTATTGTTAACTACATATGGTT | | 1081 |

Figure 5

β Actin

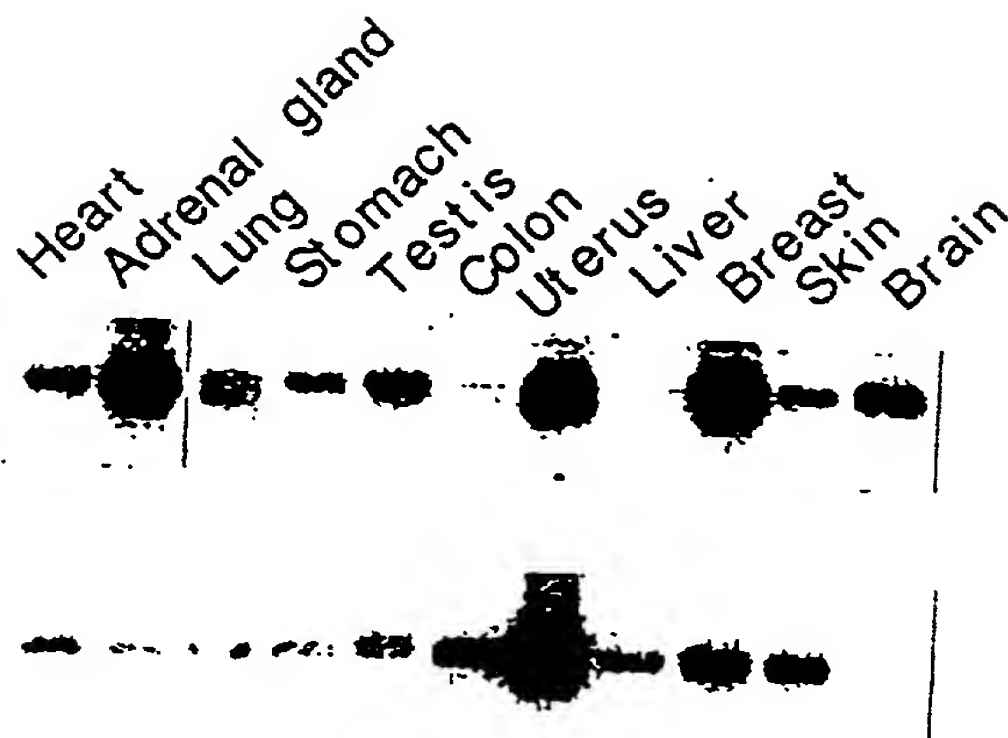


Figure 6

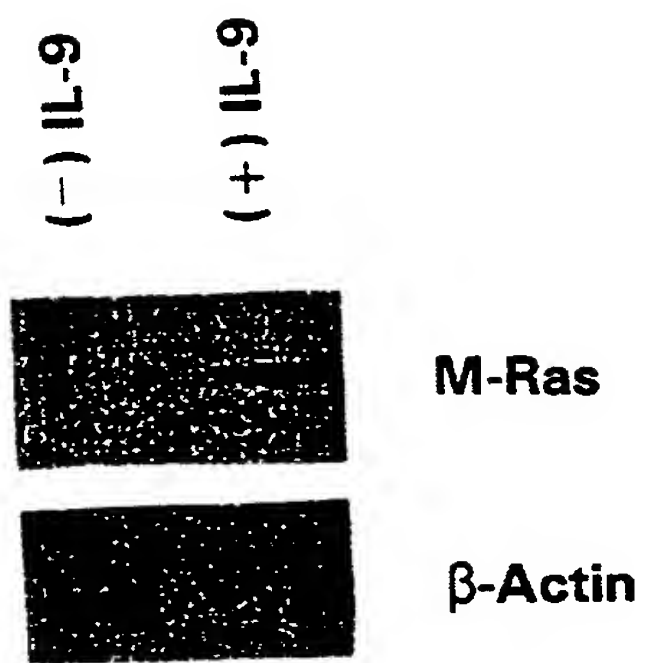


Figure 7

| | Constitutively Activated | | | Dominant Negative | |
|-------|--------------------------|--------------------|--------------------|--------------------|----------------------|
| M-Ras | M-Ras-1 | M-Ras-2 | M-Ras-3 | M-Ras-4 | M-Ras-5 |
| | G22→V22 GGT→GTT | Q71→K71 CAG→AAA | G22→K22 GGT→AAG | S27→N27 AGT→AAT | C205→S205 TGT→TCT |

Figure 8

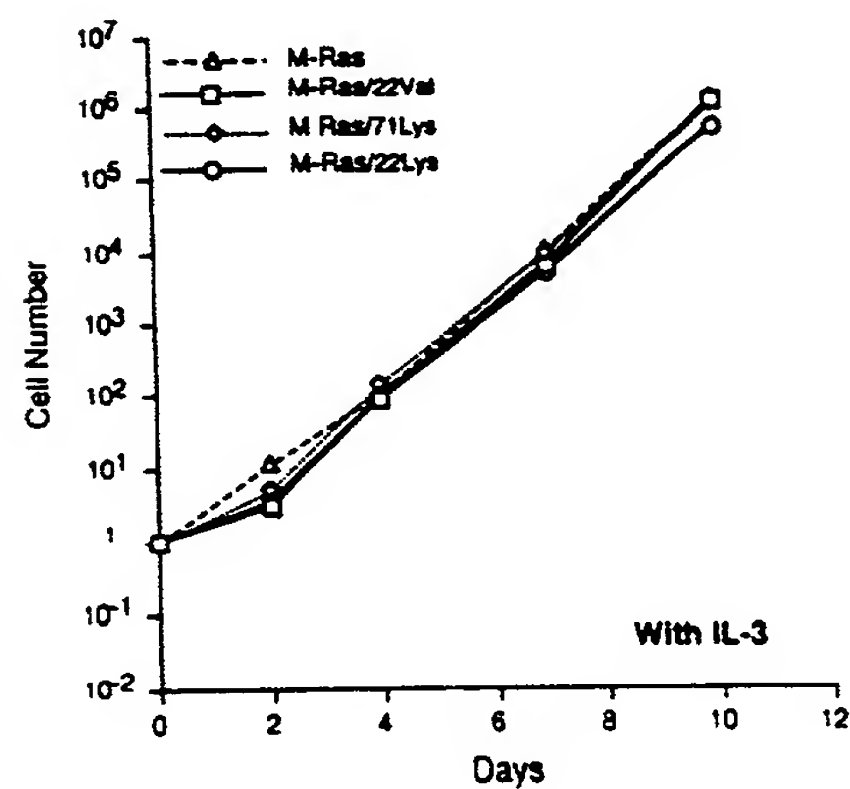
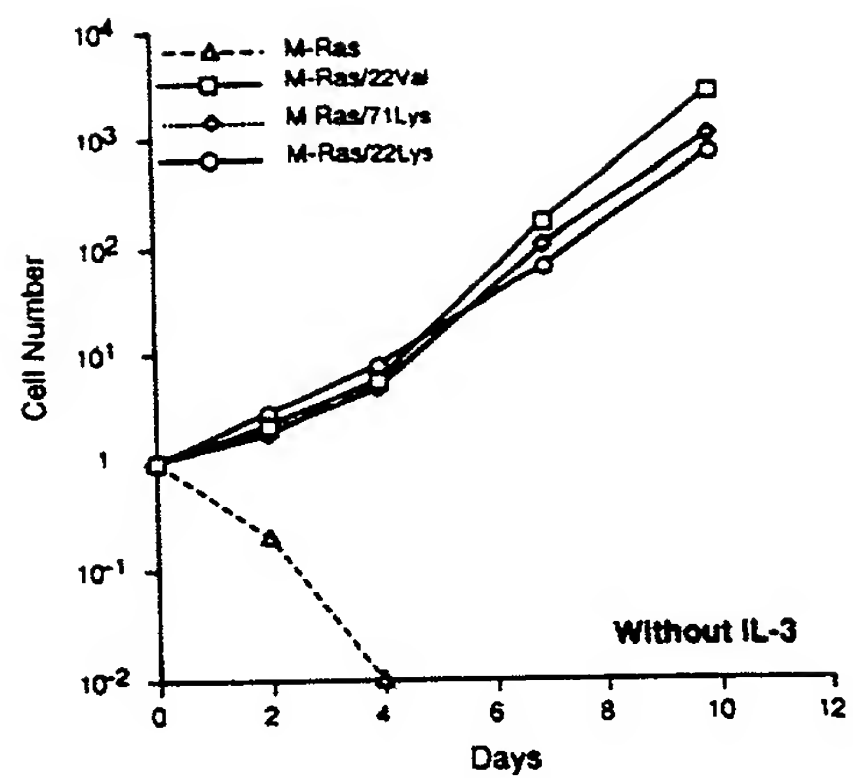


Figure 9

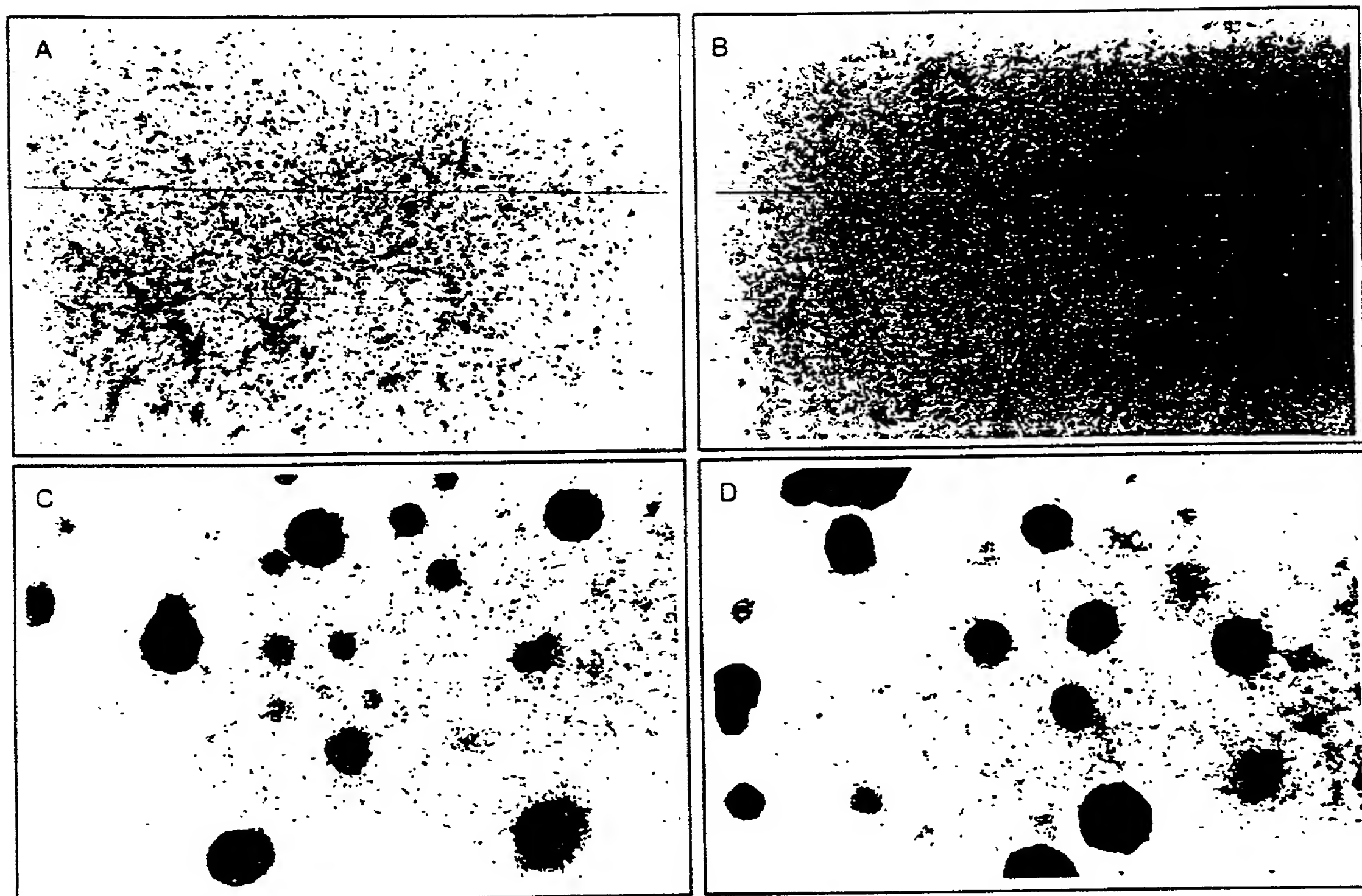


Figure 10

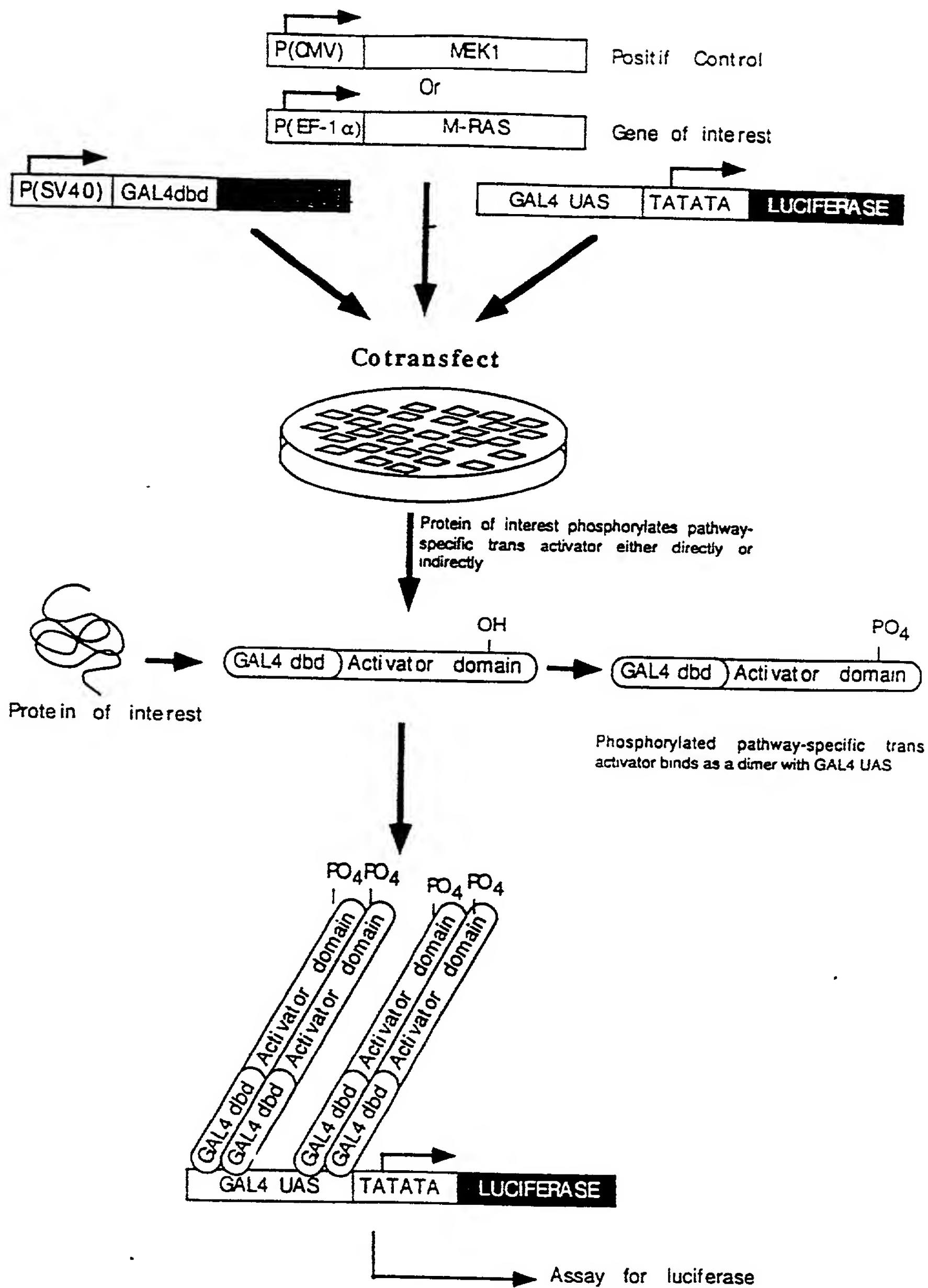


Figure 11

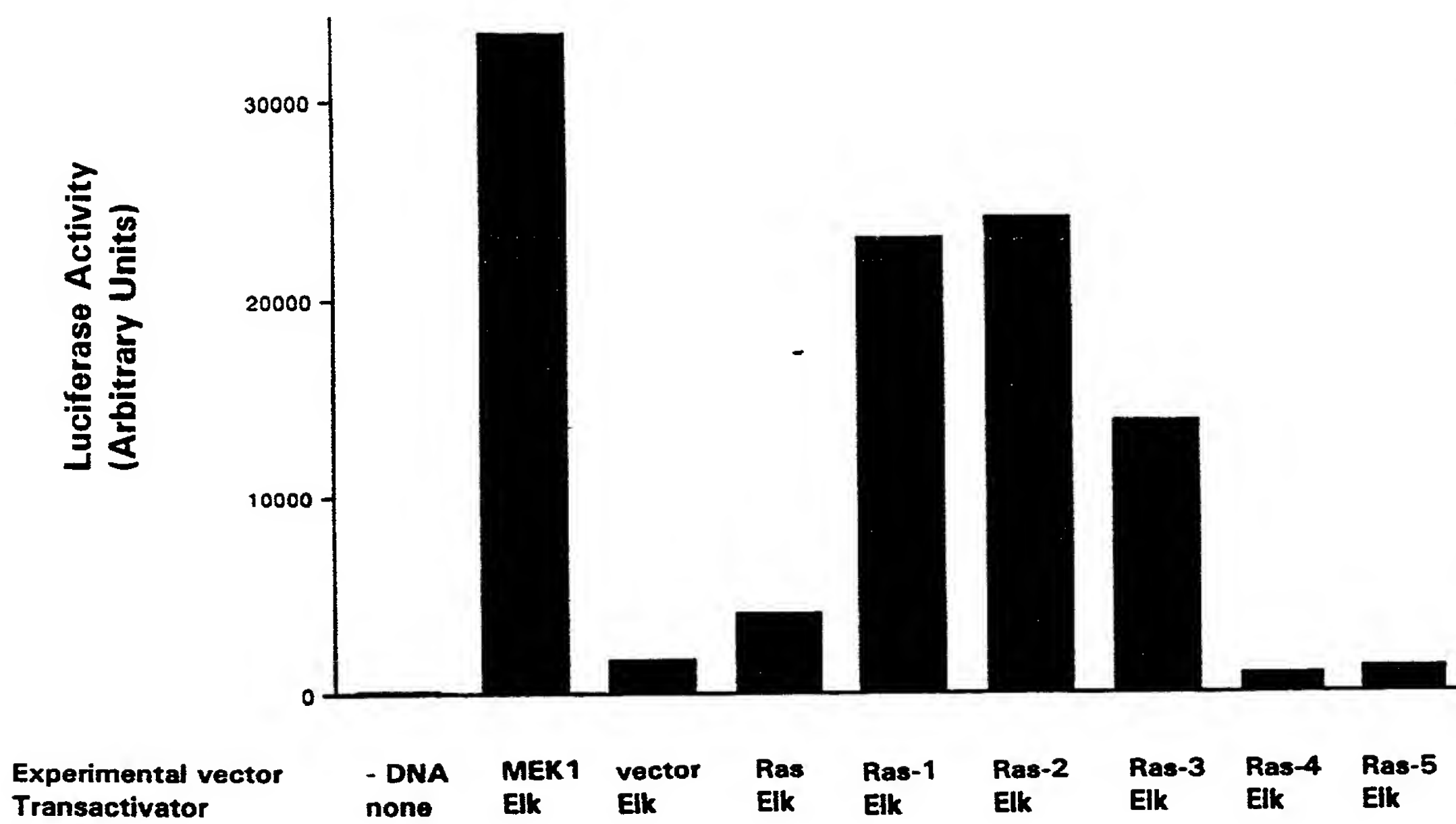


Figure 12

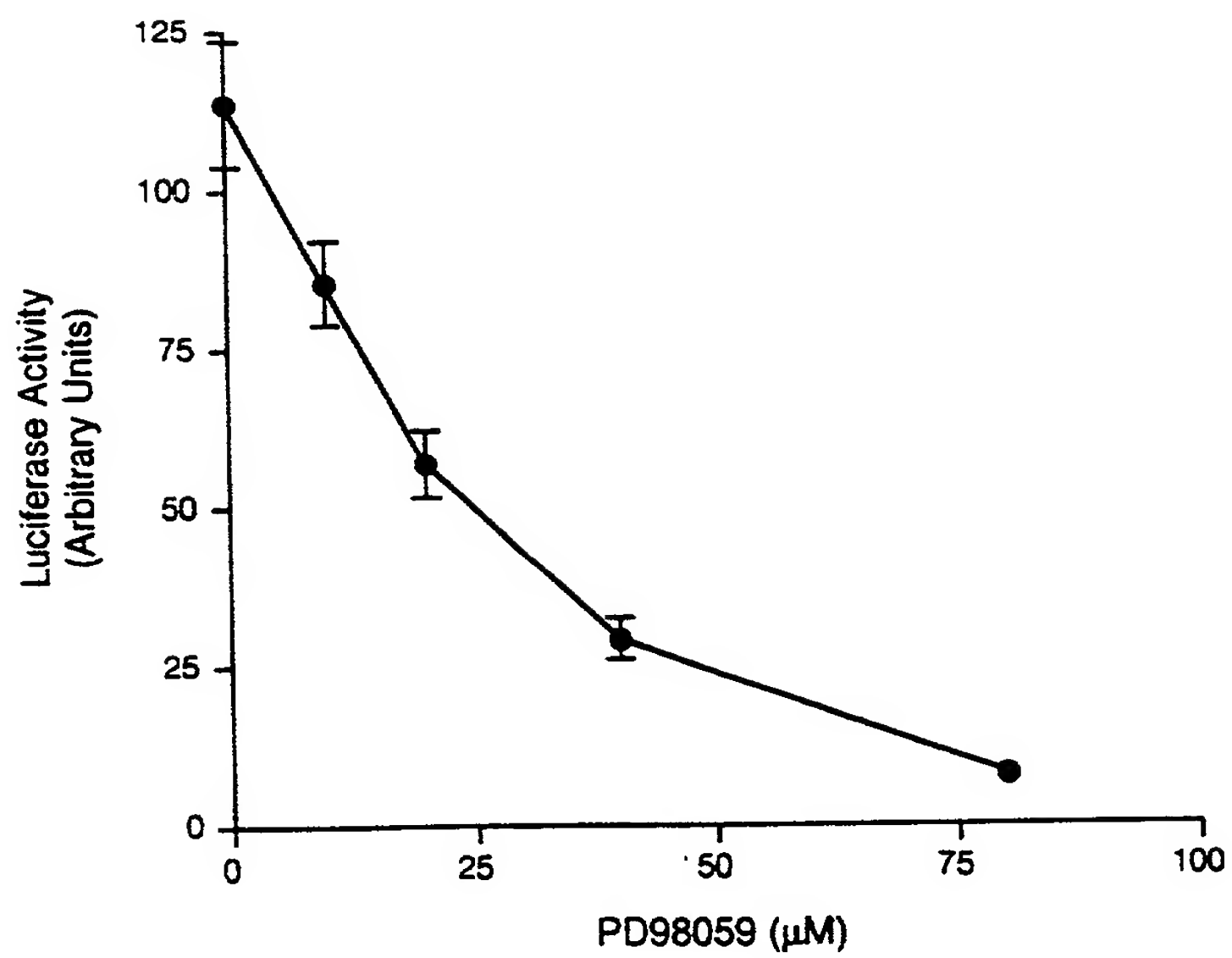


Figure 13

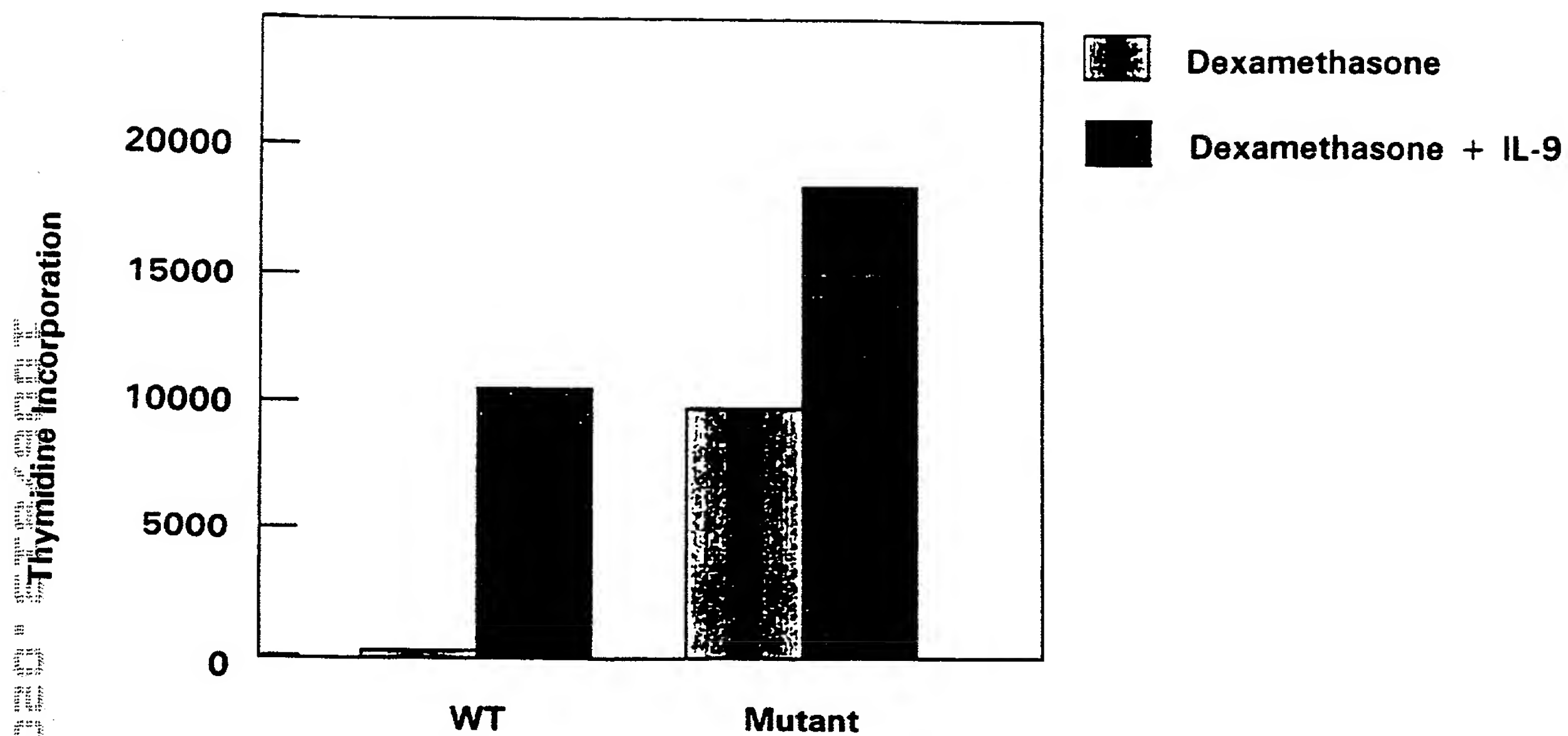


Figure 14

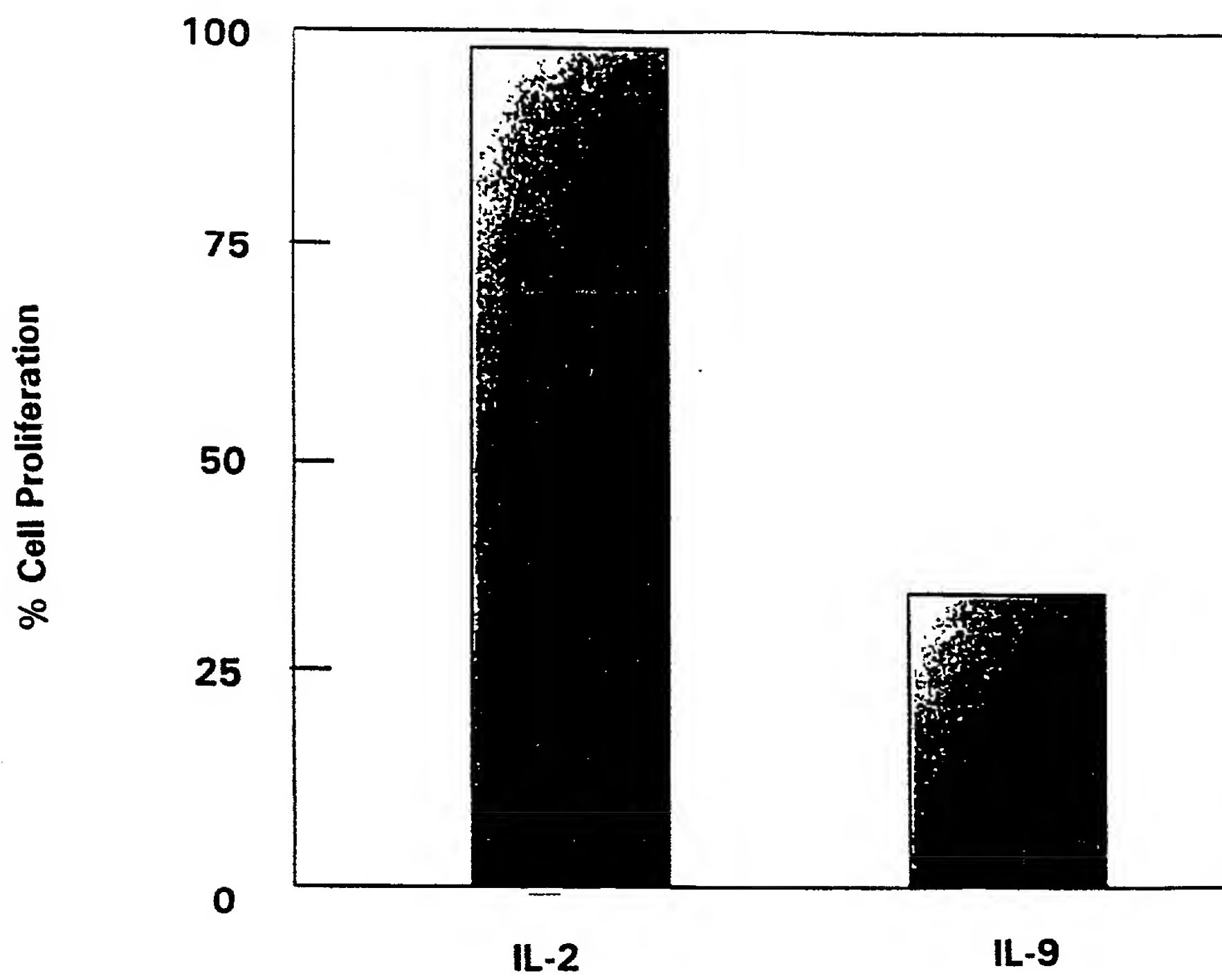


Figure 15

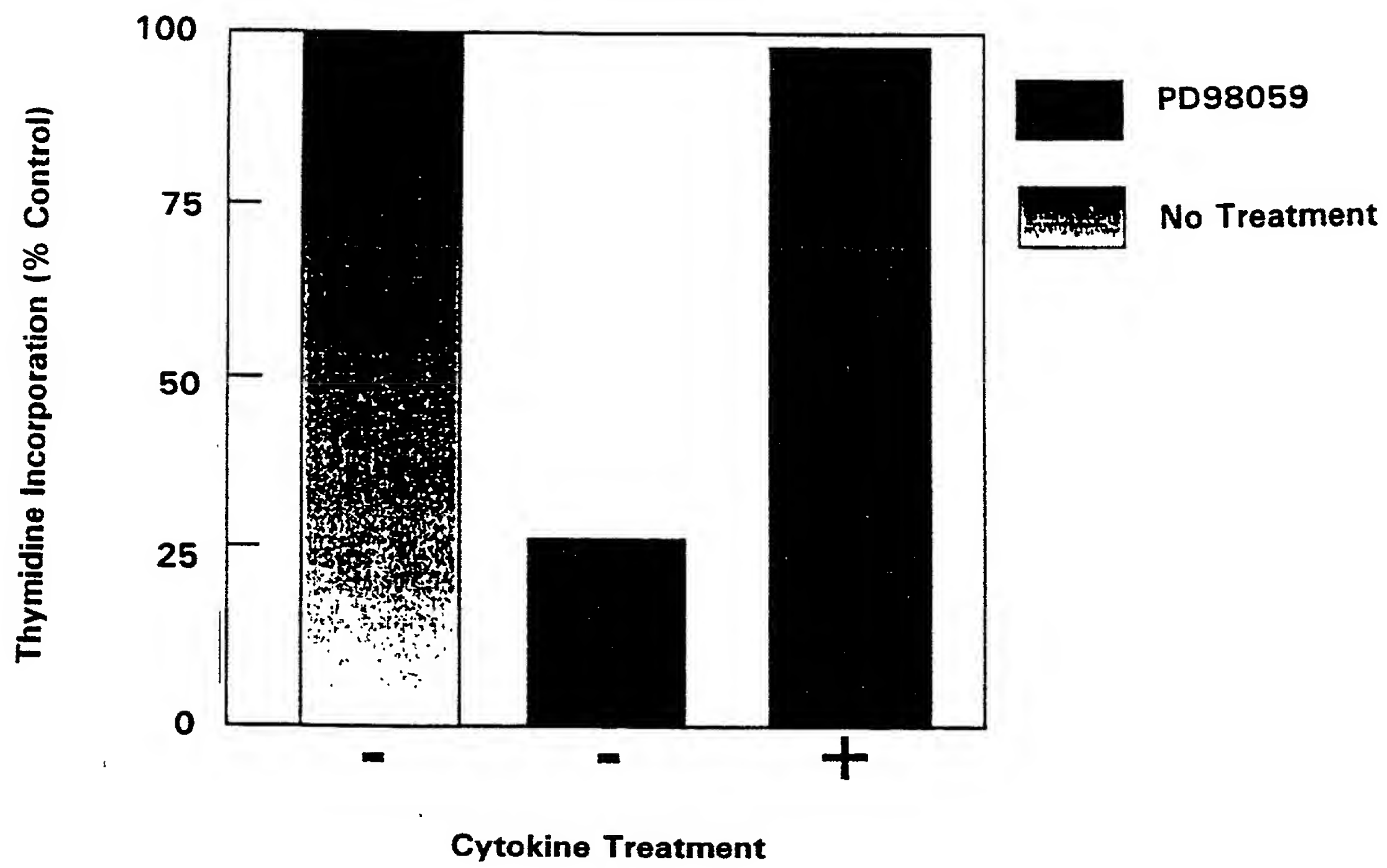


Figure 16

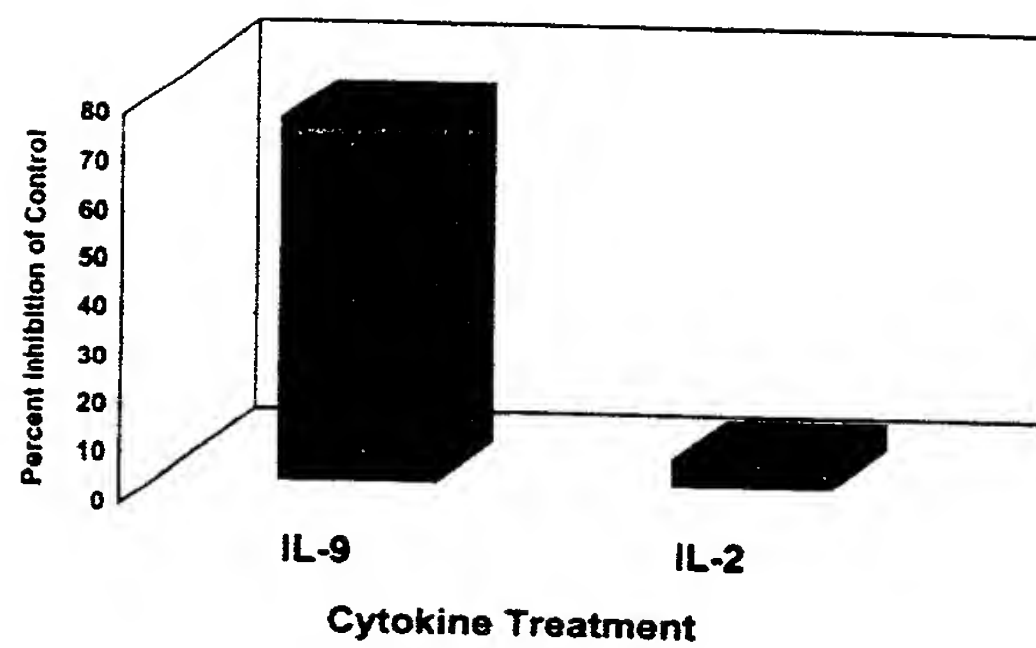


Figure 17

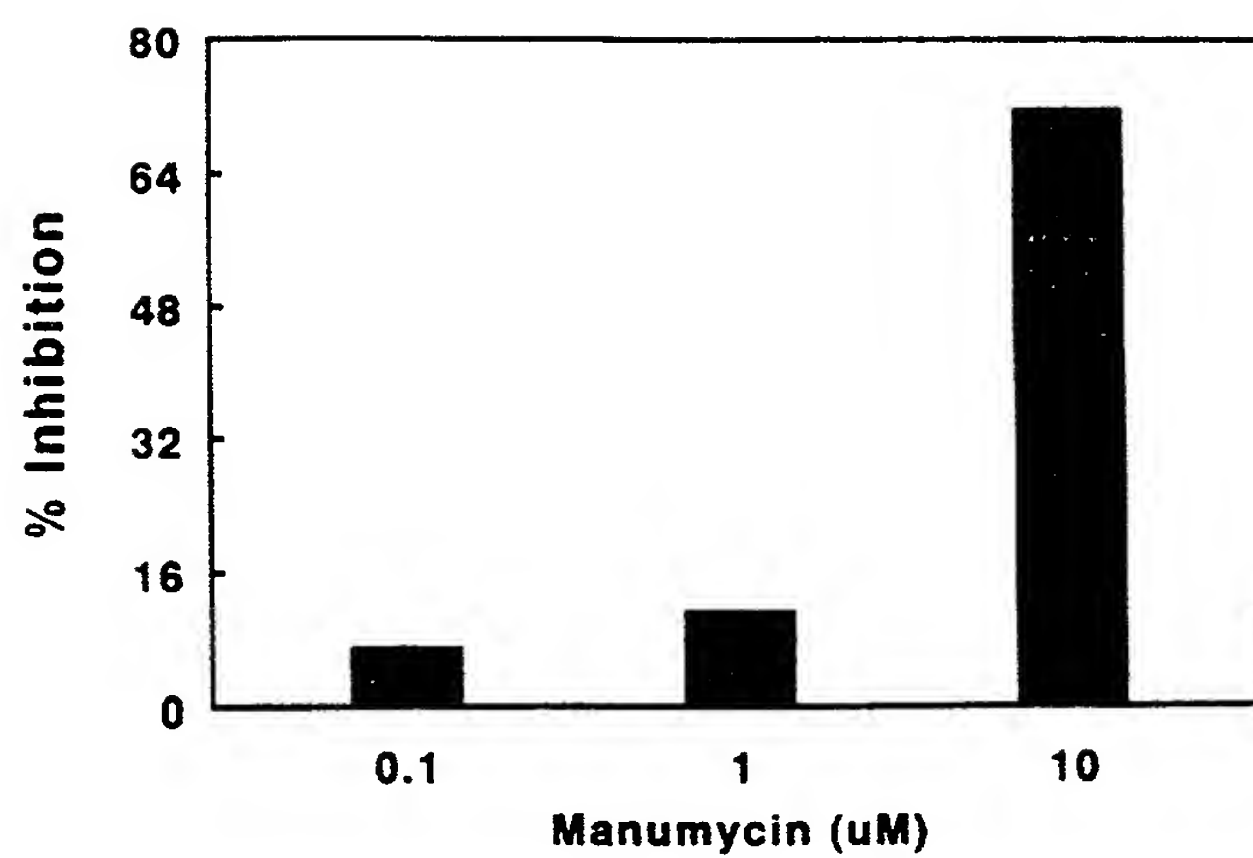


Figure 18

Effect of Lovastatin on the Proliferation of TS2 Cells

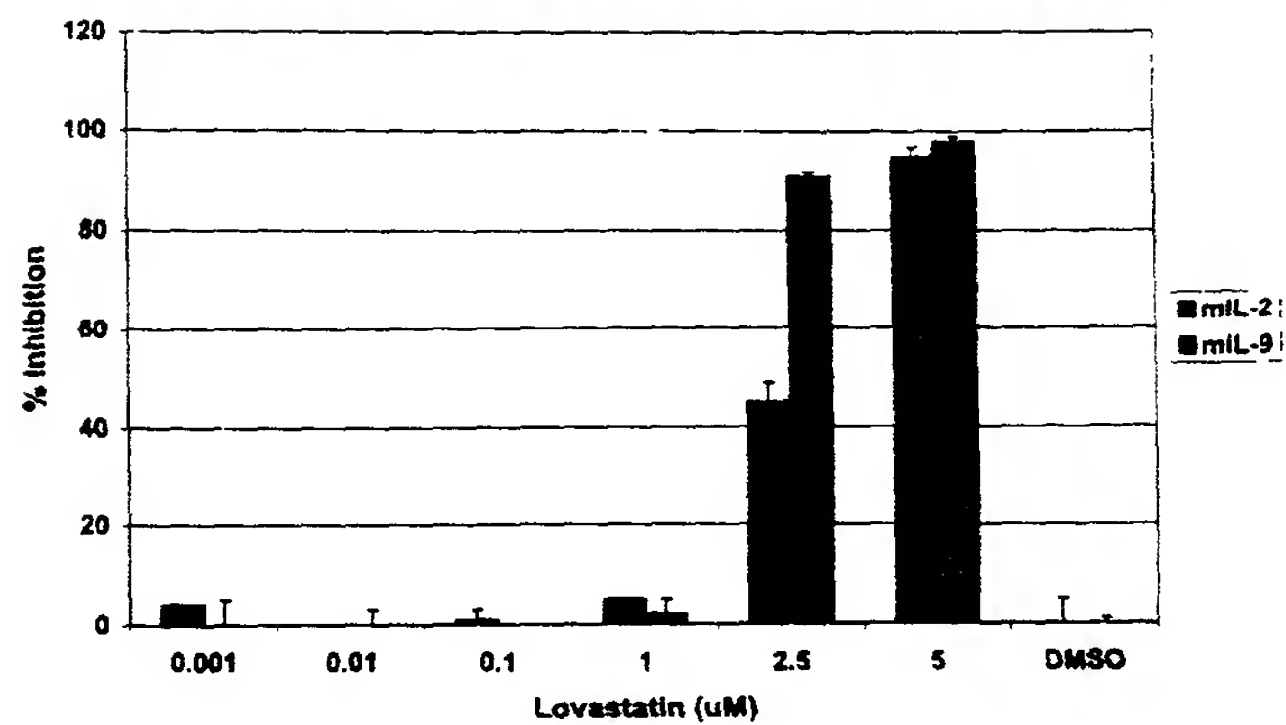
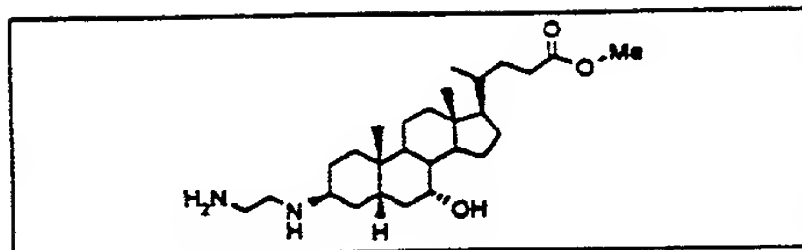
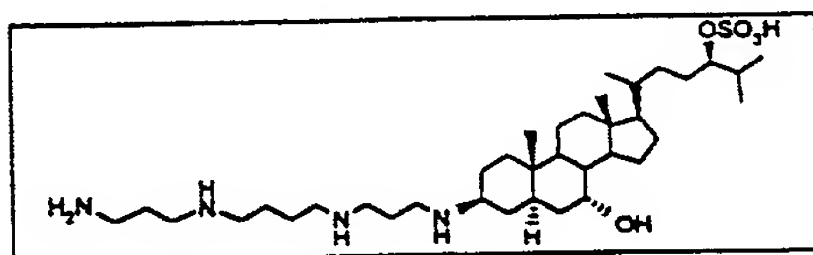


Figure 19

1409



1436



1569

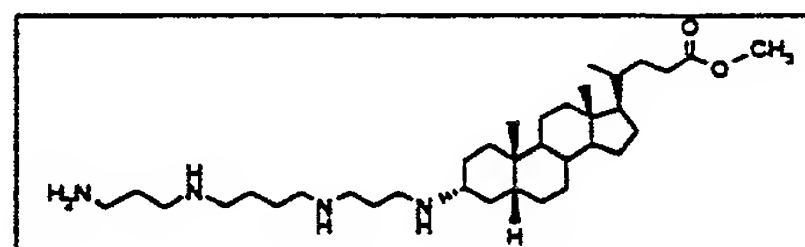


Figure 20

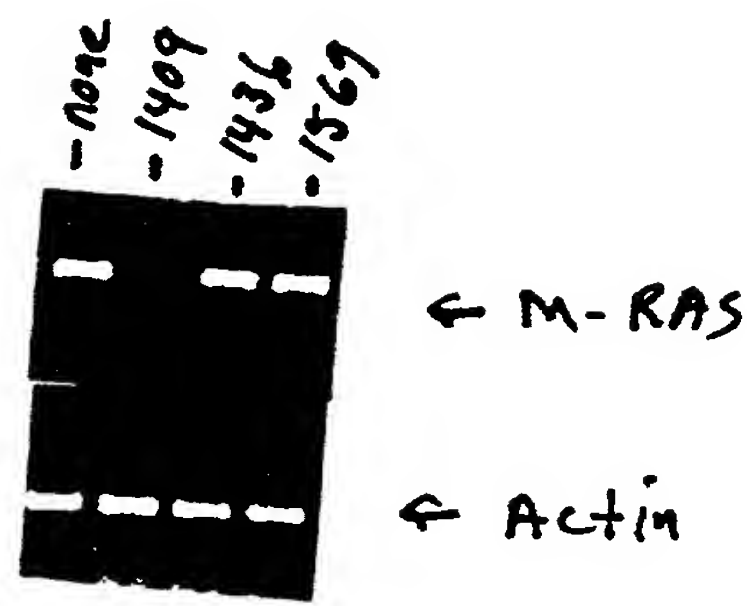


Figure 21

Lovastatin Inhibition of M-RAS Prenylation

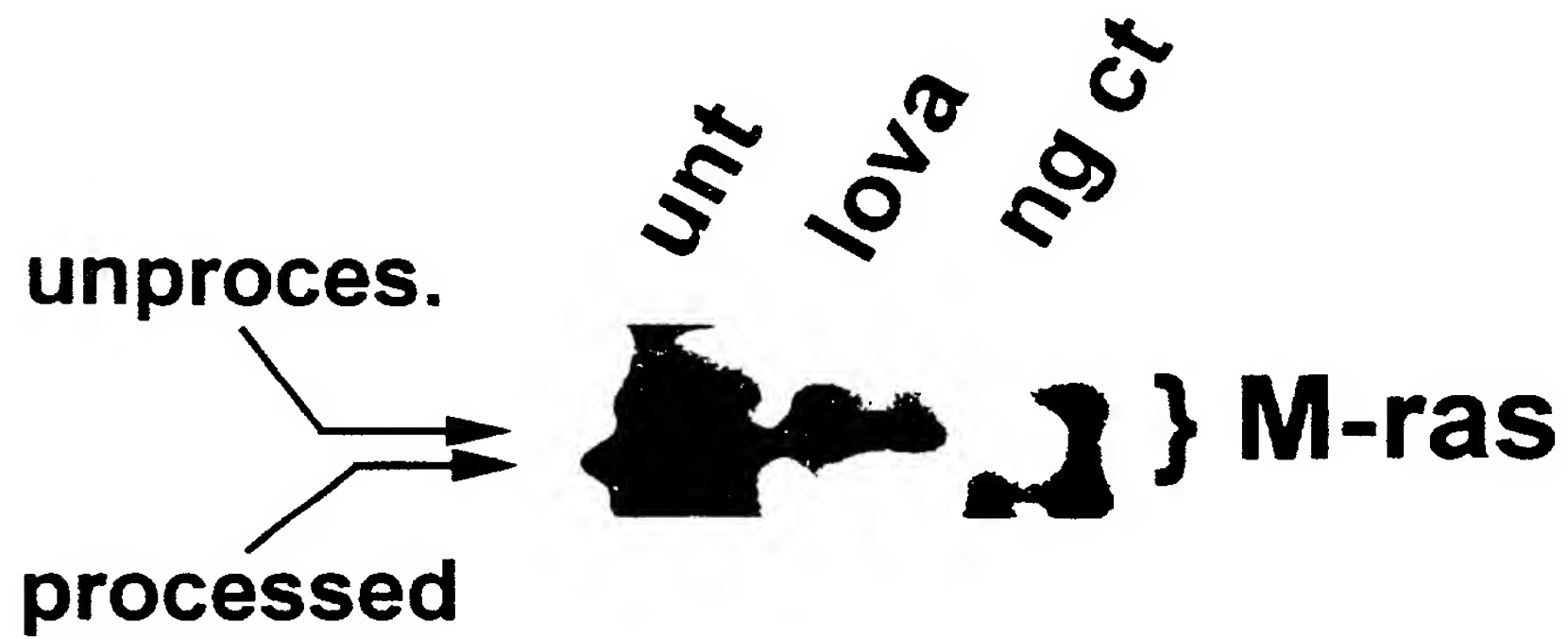


Figure 22